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A facile synthesis of new tetrahydropyrido[4,3-*d*]pyrimidine derivatives

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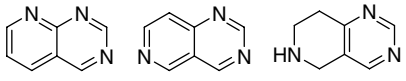
Abstract—The one-pot reaction of 1-benzylpiperidin-4-one with different nitriles in the presence of triflic anhydride affords substituted tetrahydropyrido[4,3-*d*]pyrimidines. Reaction with methylthiocyanate forms the corresponding methylthio substituted tetrahydropyridopyrimidines which can be easily converted into dimethoxy and dicarbonyl derivatives.

The pyridopyrimidines are the most important and investigated compounds among the family of the pyridodiazines. These compounds have found many applications due to their medicinal properties such as antibacterials,[1] antiallergics,[2] inhibitors of enzyme adenosine kinase[3] or dihydrofolate reductase,[4] and irreversible inhibitors of epidermal growth factor receptor.[5] The most significant synthetic procedures are focused on the preparation of the pyrido[2,3-*d*]pyrimidines (**1**) because this heterocyclic system induces an inhibition phase of the cell cycle progression.[6] In contrast, pyrido[4,3-*d*]pyrimidines (**2**) have received less attention in spite of their interesting medicinal applications.[5] 5,6,7,8-Tetrahydropyrido[4,3-*d*]pyrimidine (**3**) and related compounds have been used as starting materials for the multi-step synthesis of tetrahydropteroic acid derivatives.[7] On the other hand, substituted diamino-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidines were tested due to the ability of the products to inhibit dihydrofolate reductase from *Pneumocystis carinii* and *Toxoplasma gondii*.[8] Tetrahydropyridopyrimidines (THPPm) derivatives are used as starting materials to react with terminal alkynes forming tetrahydropyrimidino[4,5-*d*]azocines.[9]

The classical synthesis of the pyridopyrimidine ring system begins with either pyridine or pyrimidine which is modified to establish the other ring.[10] Generally, this methodology involves tedious multi-step procedures based on the synthesis of starting materials not easy to prepare.[11]



1 **2** **3**

We describe herein a facile one-pot synthesis of pyrido[4,3-*d*]pyrimidine derivatives based on the reaction of 1-benzylpiperidin-4-one with different nitriles in the presence of triflic anhydride.

In previous papers, we have reported the synthesis of a great variety of heterocyclic systems based on the reaction of carbonyl compounds with nitriles in the presence of triflic anhydride.[12] We have found that, the reaction of 1-benzylpiperidin-4-one (**4**) with different nitriles and Tf_2O under mild conditions affords 2,4-disubstituted-*N*-trifluoromethylsulfonyltetrahydropyrido[4,3-*d*]-pyrimidines (**5**) in moderate yields (Scheme 1 and Table 1).

Although esters and lactones react directly with nitriles and Tf_2O to form alkoxy- and pyranopyrimidines, respectively,[13] the nitrogen atoms of amides and lactames need to be protected to avoid their reaction with triflic anhydride.[14] It is important to note that the presence of a trifluoromethylsulfonyl group attached to the nitrogen atom of the tetrahydropyridine ring such as

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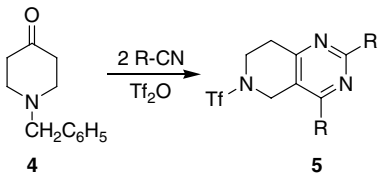


4 5

Scheme 1.

Table 1. Tetrahydropyridopyrimidines **5** prepared

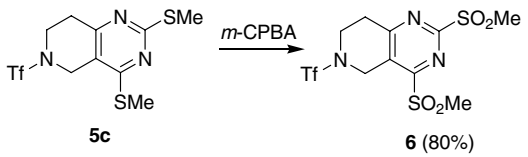
Nitrile:R-CN	Compound	Yield[a] (%)
R = Me	**5a**	65
R = 4-MePh	**5b**	45
R = MeS	**5c**	53

[a] Yield of isolated product.

in compounds **5** can only be explained by a displacement of the benzyl group by the triflic anhydride. Traces of TfOH acid formed during the reaction probably catalyze the debenzylation reaction to form the amine, which subsequently reacts with Tf_2O affording the *N*-trifluoromethylsulfonyl derivative.[15–19]

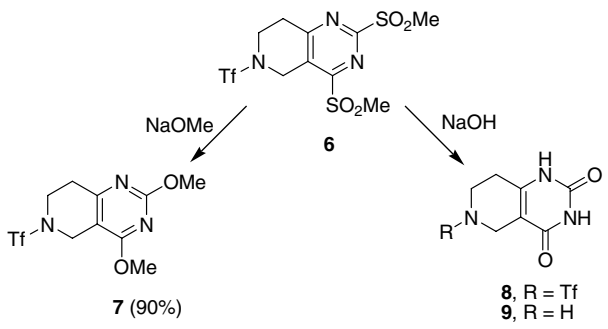
The bis(methylthio) substituted pyridopyrimidine **5c** can be used as starting material to prepare other interesting derivatives. Because methylthio groups on the pyrimidine rings can be removed only using harsh conditions, the transfunctionalization of pyridopyrimidine **5c** requires a prior oxidation to form a better leaving group such as methylsulfonyl group. Thus, the reaction of **5c** with *m*-CPBA affords the corresponding disulfone **6** in good yield[20,21] (Scheme 2).

The reaction of disulfone **6** with sodium methoxide leads to the formation of dimethoxy derivative **7** in good yield where only the two sulfonyl groups attached to a carbon atom were displaced leaving the *N*-Tf group unchanged. In contrast, the reaction of **6** with sodium hydroxide



5c **6** (80%)

Scheme 2.



7 (90%) **8**, R = Tf; **9**, R = H

Scheme 3.

affords a mixture of the uracil derivatives **8** and **9** (Scheme 3). In this case, compound **9** results from the total hydrolysis of the sulfonyl groups.[22–26]

In summary, we have prepared an interesting class of heterocyclic compounds from easily available starting materials opening a new synthetic way to obtain these substances. The results confirm the great versatility of the reaction of carbonyl compounds with nitriles in the presence of triflic anhydride.

Acknowledgements

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15. General procedure for the preparation of pyridopyrimidines **5**: A mixture of 1-benzylpiperidin-4-one (**4**) (0.5 g, 2.64 mmol) and 6.35 mmol of the corresponding nitrile dissolved in 30 mL of CH_2Cl_2 was cooled at 0 °C. Triflic anhydride (0.52 mL, 3.17 mmol) in 15 mL of CH_2Cl_2 was added dropwise and the reaction mixture stirred 24 h at room temperature. The reaction mixture was hydrolyzed with aqueous $NaHCO_3$, the organic layer washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue purified by column chromatography (hexane/ethyl acetate 9:1). The crude product was recrystallized.
16. The quadrupolar relaxation promoted by the nitrogen atom of the tetrahydropyridine ring produces a broadening of the methylene groups signals. Thus, the CH_2 groups at C5 and C7 appear as broad signals from which coupling constants often cannot be observed.
17. Characterization data for 2,4-dimethyl-6-[(trifluoromethyl)sulfonyl]-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine **5a**: undistillable oil, ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 2.37 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 3.01 (t, $J = 6$ Hz, 2H, H8), 3.80 (bs, 2H, H7), 4.54 (bs, 2H, H5) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 20.9 (CH_3), 25.5 (CH_3), 31.7 (CH_2, C8), 43.6 (CH_2, C7), 44.3 (CH_2, C5), 111.8 (q, CF_3, $J = 320$ Hz), 119.6 (C4a), 160.3 (C4), 163.4 (C2), 166.1 (C8a) ppm; MS (EI, 70 eV): *m*/*z* 295 ($M^{\cdot+}$, 100), 162 (M−Tf, 60), 105 (13), 91 (21); Anal. Calcd for $C_{10}H_{12}F_3N_3O_2S$: C, 40.68; H, 4.10; N, 14.23; S, 10.86. Found: C, 40.89; H, 3.94; N, 14.09; S, 10.69.
18. Characterization data for 2,4-bis(4-methylphenyl)-6-[(trifluoromethyl)sulfonyl]-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine **5b**: mp 154–155 °C (MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 2.42 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.26 (m, 2H, H8), 3.94 (m, 2H, H7), 4.71 (bs, 2H, H5), 7.30, 7.50 (AA′XX′system 4H, Ar–H), 7.33, 8.44 (AA′XX′system, 4H, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 21.4 (CH_2), 21.5 (CH_2), 32.2 (CH_2, C8), 44.0 (CH_2, C7), 45.7 (CH_2, C5), 112.0 (q, CF_3, $J = 318$ Hz), 119.6 (C4a), 128.3, 128.5, 129.3, 129.6, 134.1, 134.4, 140.3, 141.2 (C arom), 162.1 (C4), 163.0 (C2), 164.1 (C8a) ppm; MS (EI, 70 eV): *m*/*z* 447 ($M^{\cdot+}$, 28), 314 (M−Tf, 100); Anal. Calcd for $C_{22}H_{20}F_3N_3O_2S$: C, 59.05; H, 4.51; N, 9.39; S, 7.17. Found: C, 58.91; H, 4.44; N, 9.30; S, 7.07.
19. Characterization data for 2,4-bis(methylthio)-6-[(trifluoromethyl)sulfonyl]-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine **5c**: mp 64–65 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 2.57 (s, 3H, SCH_3), 2.63 (s, 3H, SCH_3), 2.98 (t, $J = 5.7$ Hz, 2H, H8), 3.80 (m, 2H, H7), 4.42 (s, 2H, H5) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 12.3 (SCH_3), 14.1 (SCH_3), 31.2 (CH_2, C8), 43.4 (CH_2, C7), 43.6 (CH_2, C5), 111.8 (q, $J = 320$ Hz), 116.6 (C4a), 158.0 (C4), 167.6 (C2), 169.8 (C8a) ppm; MS (EI, 70 eV): *m*/*z* 359 ($M^{\cdot+}$, 100), 344 (M−CH_3, 11), 226 (M−Tf, 84); Anal. Calcd for $C_{10}H_{12}F_3N_3O_2S_3$: C, 33.42; H, 3.37; N, 11.69; S, 26.77. Found: C, 33.33; H, 3.25; N, 11.59; S, 26.67.
20. The oxidation of **5c** with *m*-CPBA to form **6** was carried out according to the methods previously reported.[12]
21. Characterization data for 2,4-bis(methylsulfonyl)-6-[(trifluoromethyl)sulfonyl]-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine **6**: mp 171–172 °C (MeOH); ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD, 25 °C) δ: 3.31 (s, 3H, SO_2CH_3), 3.40 (s, 3H, SO_2CH_3), 3.60 (m, 2H, H8), 3.88 (m, 2H, H7), 5.13 (s, 2H, H5) ppm; ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD, 25 °C) δ: 32.9 (C8), 39.1 (SO_2CH_3), 39.5 (SO_2CH_3), 42.6 (C7), 43.3 (C5), 112.2 (q, CF_3, $J = 321$ Hz), 116.5 (C4a), 158.0 (C4), 167.4 (C2), 169.8 (C8a) ppm; MS (EI, 70 eV): *m*/*z* 423 ($M^{\cdot+}$, 4), 290 (M−Tf, 100), 228 (32); Anal. Calcd for $C_{10}H_{12}F_3N_3O_6S_3$: C, 28.37; H, 2.86; N, 9.92; S, 22.72. Found: C, 28.25; H, 2.77; N, 9.80; S, 22.55.
22. The methanolysis of **6** to obtain **7** was carried out following procedures previously reported.[12a]
23. Characterization data for 2,4-dimethoxy-6-[(trifluoromethyl)sulfonyl]-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine **7**: mp 108–109 °C (MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ: 2.91 (t, $J = 6$ Hz, 2H, H8), 3.79 (m, 2H, H7), 3.96 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.45 (s, 2H, H5) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ: 31.4 (CH_2, C8), 42.4 (CH_2, C7), 43.7 (CH_2, C5), 54.2 (OCH_3), 54.8 (OCH_3), 111.6 (q, CF_3, $J = 319$ Hz), 116.6 (C4a), 158.0 (C4), 167.4 (C2), 169.7 (C4a) ppm; MS (EI, 70 eV): *m*/*z* 327 ($M^{\cdot+}$, 55), 296 (M−OCH_3, 12), 193 (M−TfH, 100); Anal. Calcd for $C_{10}H_{12}F_3N_3O_4S$: C, 36.70; H, 3.70; N, 12.84; S, 9.80. Found: C, 36.60; H, 3.61; N, 12.77; S, 9.69.
24. The basic hydrolysis of **6** was carried out according reported methods.[12a] Analysis of the reaction mixture by NMR and HPLC–MS-ESI reveals the presence of **8** and **9** in ratio 1:0.6, respectively, and 70% overall yield.
25. Characterization data for 6-[(trifluoromethyl)sulfonyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione **8**. ^{1}H NMR (DMSO-d_6) δ: 2.70 (t, $J = 6$ Hz, 2H, H8), 3.75 (m, 2H, H7), 4.19 (m, 2H, H5), 10.80 (s, 1H, NH), 11.04 (s, 1H, NH), 11.27 (s, 1H, NH) ppm; MS (ESI): 300 $[M+H]^+$.
26. Characterization data for 5,6,7,8-tetrahydropyrido[4,3-*d*]-pyrimidine-2,4-(1*H*,3*H*)-dione **9**. ^{1}H NMR (DMSO-d_6) δ: 2.57 (m, $J = 6.5$ Hz, 2H, H8), 3.45 (m, 2H, H7), 4.19 (m, 2H, H5), 11.0 (1H, NH), 11.35 (1H, NH) ppm; MS(ESI): 168 $[M+H]^+$.